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United States Environmental Protection Agency
Office of Pollution Prevention and Toxics

HFC-134a (1,1,1,2-TETRAFLUOROETHANE)
CAS Reg. No. 811-97-2

PROPOSED ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

"PUBLIC DRAFT"

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee to develop Acute Exposure Guideline Levels (AEGLs) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent ceiling exposure values for the general public and are applicable to emergency exposure periods ranging from less than 1 hour to 8 hours. Three AEGLs will be developed for each of five exposure periods (10 minutes, 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. The National Advisory Committee believes that the recommended exposure levels will be protective of the general population including sensitive and susceptible individuals. This classification includes infants and children. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm and mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience notable discomfort. Airborne concentrations below AEGL-1 represent exposure levels that could produce mild odor, taste, or other sensory irritation.

AEGL-2 is the airborne concentration (expressed as ppm and mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience irreversible or other serious, long-lasting effects or impaired ability to escape. Airborne concentrations below AEGL-2 but at or above AEGL-1 represent exposure levels which may cause notable discomfort.

AEGL-3 is the airborne concentration (expressed as ppm and mg/m^3) of a substance at or above which it is predicted that the general population, including "susceptible" but excluding "hypersusceptible" individuals, could experience life-threatening effects or death. Airborne concentrations below AEGL-3 but at or above AEGL-2 represent exposure levels which may cause irreversible or other serious, long-lasting effects or impaired ability to escape.

EXECUTIVE SUMMARY

1,1,1,2-Tetrafluoroethane or hydrofluorocarbon-134a (HFC-134a) has been developed as a replacement for fully halogenated chlorofluorocarbons because its residence time in the atmosphere is shorter and its ozone depleting potential is insignificant. HFC-134a may be used in refrigeration and air conditioning systems, as a blowing agent for polyurethane foams, and as a propellant for medical aerosols. Yearly production is estimated at 175,000 tons.

HFC-134a has a very low acute inhalation toxicity. Its acute inhalation effects have been studied with human subjects and several animal species including the monkey, dog, rat, and mouse. In addition, studies addressing repeated and chronic exposures, genotoxicity, carcinogenicity, neurotoxicity, and cardiac sensitization were also available. At high concentrations, halogenated hydrocarbons may produce cardiac arrhythmias; this sensitive endpoint was considered in development of AEGL values.

Adequate data were available for development of the three AEGL classifications. Inadequate data were available for determination of the relationship between concentration and time for a fixed effect. Based on the observations that 1) blood concentrations in humans rapidly approach equilibrium with negligible metabolism and tissue uptake and 2) the endpoint of cardiac sensitization is a blood concentration-related threshold phenomenon, derived values for each AEGL classification were flat-lined across time.

The AEGL-1 concentration was based on a 1-hour no-effect concentration of 8000 ppm in human subjects (Emmen and Hoogendijk, 1998). This concentration was without effects on lung functions, respiratory parameters, the eyes (irritation), or the heart (cardiac symptoms). Because this concentration is considerably below that causing any effect in animal studies, an intraspecies uncertainty factor of 1 was applied. Based on the fact that blood concentrations in this study appeared to be approaching equilibrium following 55 minutes of exposure and effects are determined by blood concentrations, the value of 8000 ppm was used across all time periods.

The AEGL-2 concentration was based on the no-effect concentration of 40,000 ppm for cardiac sensitization in dogs (Hardy et al., 1991). Because the cardiac sensitization test is supersensitive as the response to epinephrine is optimized (the epinephrine dose is greater than the physiological level in stressed animals by up to a factor of ten), a single intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. Cardiac sensitization is concentration dependent; duration of exposure does not influence the concentration at which this effect occurs. Using the reasoning that the concentration is the determining factor in cardiac sensitization and exposure duration is of lesser importance, the resulting value of 13,000 ppm is proposed for all time periods.

The AEGL-3 concentration was based on the concentration of 80,000 which caused marked cardiac effects but no deaths in dogs (Hardy et al., 1991). Because the cardiac sensitization test is supersensitive as the response to epinephrine is optimized (the epinephrine dose is greater than the physiological level in stressed animals by up to a factor of ten), a single intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. Cardiac sensitization is concentration dependent; duration of exposure does not influence the concentration at which this effect occurs. Using the reasoning that the concentration is the determining factor in cardiac sensitization and exposure duration is of lesser importance, the resulting value of 27,000 ppm is proposed for all time periods.

Based on the extensive data base involving both human and animal exposures and use of the most sensitive endpoint in the studies, confidence in the AEGL values is high. Values are summarized in the table below.

SUMMARY TABLE OF PROPOSED AEGL VALUES						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	No effects - humans (Emmen and Hoogendijk, 1998)
AEGL-2	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	No effect, cardiac sensitization - dogs (Hardy et al., 1991)
AEGL-3	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	Marked effect, cardiac sensitization - dogs (Hardy et al., 1991)

Emmen, H.H., and E.M.G. Hoogendijk. 1998. Report on an ascending dose safety study comparing HFA-134a with CFC-12 and air, administered by whole-body exposure to healthy volunteers. MA-250B-82-306, TNO Report V98.754, The Netherlands Organization Nutrition and Food Research Institute, Zeist, The Netherlands.

Hardy, C.J., I.J. Sharman, and G.C. Clark. 1991. Assessment of cardiac sensitisation potential in dogs: comparison of HFA 134a and A12. Report No. CTL/C/2521. Huntingdon Research Centre, Huntingdon, Cambridgeshire, U.K.

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

LIST OF TABLES

1. INTRODUCTION

Hydrofluorocarbons (HFCs) are being increasingly substituted for chlorofluorocarbons (CFCs) in industry because the substitution of hydrogen for halogen in methane and ethane reduces residence time in the stratosphere compared to completely halogenated compounds and therefore causes less depletion of ozone. The contribution of radicals formed by the atmospheric degradation of 1,1,1,2-tetrafluoroethane (HFC-134a) to ozone depletion is insignificant and its global warming potential is much lower than that of CFCs (Ravishankara et al., 1994; ECETOC, 1995).

HFC-134a has been developed as a replacement for fully halogenated chlorofluorocarbons and for partially halogenated hydrochlorofluorocarbons. Its primary use is in refrigeration and air conditioning systems in which it is used alone or as a component of blends. It has been used or is being considered for use as a blowing agent for polyurethane foams and is being used as a propellant for medical aerosols (ECETOC, 1995; Harrison et al., 1996).

HFC-134a is produced commercially by 1) the hydrofluorination of trichloroethylene via 1-chloro-1,1,1-trifluoroethane, 2) isomerization/hydrofluorination of 1,1,2-trichloro-1,2,2-trifluoroethane to 1,1-dichloro-1,2,2,2-tetrafluoroethane followed by hydrodechlorination, and 3) hydrofluorination of tetrachloroethylene to 1-chloro-1,2,2,2-tetrafluoroethane and subsequent hydrodechlorination to tetrafluoroethane (ECETOC 1994). It is manufactured by 13 companies in the United States: Airso Company, Inc., Neodesha, KS; AlliedSignal Inc., Morristown, NJ; Acctech, LLC, Nanuet, NY; Chemtronics, Inc., Kennesaw, GA; E.I. duPont de Nemours & Co., Inc., Wilmington, DE; Falcon Safety Products, Inc., Somerville, NJ; Hoechst Celanese Corp., Charlotte, NC; ICI Americas Inc., Wilmington, DE; Miller-Stephenson Chemical Co., Danbury, CT; Texwipe Co., Upper Saddle River, NJ; Techspray, Amarillo, TX; Valvoline, Inc., Lexington, KY; and Wescor, Inc., Logan, UT (LMES 1995). World production capacity was estimated at 175,000 tons/year in the early 1990s (ECETOC, 1995). Production is estimated at 300,000 tons/year by 2020.

HFC-134a is a nonflammable colorless gas or liquified gas with a faint ethereal odor. The vapor is heavier than air and can displace air in confined spaces (ECETOC, 1995). Additional chemical and physical properties are listed in Table 1.

Experimental studies with human subjects and several mammalian species (monkey, dog, rat, mouse, and rabbit) were located. Animal studies addressed neurotoxicity, genotoxicity, carcinogenicity, and cardiac sensitization and were conducted over acute, subchronic, and chronic exposure durations.

TABLE 1. Chemical and Physical Data

Parameter	Value	Reference
Synonyms	HFC-134a 1,1,1,2-tetrafluoroethane HFA-134a HCFC 134a R-134a	ECETOC, 1995, HSDB, 1998
Molecular formula	$C_2H_2F_4$	ECETOC, 1995
Molecular weight	102.03	HSDB, 1998
CAS Registry Number	811-97-2	HSDB, 1998
Physical state	gas or liquified gas	ECETOC, 1995
Color	colorless	ECETOC, 1995
Solubility in water	1 g/L	ECETOC, 1995
Vapor pressure	4730 mm Hg @25°C	HSDB, 1998
Vapor density	3.52	ECETOC, 1995
Melting point	-108°C	ECETOC, 1995
Boiling point	-26°C	ECETOC, 1995
Odor	faint ethereal	ECETOC, 1995
Odor threshold	not available	
Conversion factors	1 ppm = 4.25 mg/m^3 1 mg/m^3 = 0.24 ppm	ECETOC, 1995

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

Although deaths from exposure to CFCs have occurred during refrigeration repair, use as solvents, and aerosol propellant use and abuse (Aviate, 1994), no data specific to HFCs were located.

2.2. Nonlethal Toxicity

Eight healthy human volunteers, 4 males and 4 females, ages 20-24, were exposed individually (whole-body) to concentrations of 0 (air), 1000, 2000, 4000, or 8000 ppm for one hour in a 13.6 m^3 room (Emmen and Hoogendijk, 1998)[1]. Each subject was exposed to each concentration in a partially blind ascending order of concentration. With the exception of one 14-day interval, each exposure was separated by a period of 7 days. Chlorofluorocarbon-12 was used as a reference compound. Prior to and during exposures, blood pressure and

[1]The protocol was approved by the Medical Ethics Testing Committee of The Netherlands Organization. Subjects signed an informed consent form.

cardiac rate and rhythm (EKG) were monitored. Lung function as indicated by peak expiratory flow was measured before and after exposures. Blood samples were taken prior to, during, and after exposure for pharmacokinetic data. Clinical chemistry and hematology parameters were also recorded pre- and postexposure. The test chemical was vaporized and introduced into the air supply of the exposure chamber via a calibrated rotameter; the atmospheres were monitored with a gas monitor. Five samples were taken from each of six locations in the exposure chamber.

Atmospheres were within a few percent of nominal concentrations; the mean oxygen concentration was ~20.5%. No significant or consistent differences were found between air exposure and test chemical exposure for clinical observations, blood pressure, heart rate, peak expiratory flow, or EKG recordings. During blood sampling and blood pressure measurements, all subjects showed sinus arrhythmia pre- and postexposure. A Mobitz type I heart block was present in one subject pre-, during and post-exposure. Medical personnel did not consider this a risk and the informed subject completed the study.

CFCs are used as propellants in metered dose inhalers for the treatment of asthma. To that end, HFC-134a has been tested with human subjects using repeated inhalations. Three studies are cited here as examples of the direct inhalation from such devices. In a 28-day double blind parallel study, two groups of eight healthy non-smoking male subjects, ages 18-55, inhaled either HFC-134a propellant from a pressurized metered-dose inhaler (HFC 134a as propellant, ethanol as co-solvent and oleic acid as surfactant) or chlorofluorocarbon propellants (Harrison et al., 1996). All subjects gave written informed consent. Subjects received either four inhalations four times per day for 14 days or eight inhalations four times per day for 14 days; after 14 days the subjects were given the alternate propellant. Subjects held their breath for 10 seconds after each inhalation and waited 30 seconds between inhalations. Blood pressure, heart rate, and EKGs were recorded; pulmonary function tests were administered immediately before and 20 minutes after the first exposure on each day; blood was taken for clinical chemistry at this time on various days. No clinically significant differences from baseline occurred in blood pressure, heart rate, EKGs, pulmonary functions, hematology or serum chemistry. One subject had an elevated eosinophil count throughout the study. The most frequently reported subjective adverse effect was headache, reported by four subjects in each propellant group. This study followed an earlier study in which 12 healthy subjects also showed no adverse response to inhalation of HFC-134a (Donnell et al., 1995). In the earlier study, three subjects reported adverse events of coughing or nausea and vomiting. The relationship of these events to the dosing is unknown. When radiolabeled HFC-134a was delivered by metered dose inhalers to healthy subjects and patients with severe chronic obstructive pulmonary disease (COPD), there were no adverse effects as monitored by vital signs, pulmonary function tests, EKG, and liver function and no symptoms of upper respiratory tract irritation (Ventresca, 1995).

2.3. Developmental/Reproductive Toxicity

No studies were located regarding reproductive or developmental effects in humans after inhalation exposure to HFC-134a.

2.4. Neurotoxicity

No neurotoxic signs were reported following inhalation exposure to HFC-134a.

2.5. Genotoxicity

No information on genotoxicity in humans was located, *In vitro*, chromosome aberration assays with human lymphocytes were negative (Collins et al., 1995).

2.6. Carcinogenicity

No information on carcinogenicity in humans was located.

2.7. Summary

In a study with human volunteers exposed to concentrations up to 8000 ppm for 1 hour, no effects on lung function, clinical chemistry, hematology parameters, or heart rate or rhythm were observed. When HFC-134a was delivered directly to the respiratory tract with metered dose inhalers, no adverse effects as indicated by clinical signs, respiratory tract irritation, or heart rhythm were reported. The occurrences of headache, coughing, or nausea in some of the subjects that tested metered dose inhalers are difficult to interpret.

3. ANIMAL TOXICITY DATA

3.1 Acute Lethality

Acute lethality data are summarized in Table 2. The only species tested in these studies was the rat. In the rat, a 15-minute LC_{50} of >800,000 ppm and a 4-hour LC_{50} of >500,000 ppm have been reported (Collins, 1984). The 30-minute LC_{50} was 750,000 ppm (Rissolo and Zapp, 1967). In another study, groups of six rats were exposed to time-weighted average concentrations of 81,100, 205,200, 359,300, 566,700, 646,700, or 652,700 ppm for 4 hours (Silber and Kennedy, 1979a). The lowest lethal concentration was 566,700 ppm which resulted in the deaths of five of six rats. Two of six rats exposed to 652,700 ppm also died. Signs observed during exposures in these studies included lethargy, rapid respiration, trembling, tearing, foaming at the nose, pallor, and weight loss during the first 24 hours of the recovery period. Surviving rats appeared normal within 5 minutes after exposures and no abnormalities were present in surviving rats necropsied 14 days postexposure.

TABLE 2. Summary of Acute Lethal Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
rat	>800,000	15 minutes	LC_{50}	Collins, 1984
rat	750,000	30 minutes	LC_{50}	Rissolo and Zapp, 1967
rat	566,700	4 hours	lowest lethal concentration	Silber and Kennedy, 1979a
rat	>500,000	4 hours	LC_{50}	Collins, 1984

3.2. Nonlethal Toxicity

Results of acute exposures are summarized in Table 3.

3.2.1. Nonhuman Primates

Exposure to a concentration of 500,000 ppm induced narcosis in rhesus monkeys within 1 minute (Shulman and Sadove, 1967). Respiratory depression accompanied by multiple premature ventricular contractions occurred when concentrations exceeded 60%. Blood pressure also increased, but data were not reported.

3.2.2. Dogs

Concentrations of 700,000 and 800,000 ppm for 3 to 5 hours induced deep anesthesia in dogs, usually within 1 minute (Shulman and Sadove, 1967). Respirations remained spontaneous and blood pressure remained normal. Light anesthesia was induced at concentrations of 500,000 to 600,000 ppm. Emergence time was usually less than 2 minutes.

In another study, the effect of HFC-134a on the histamine-induced bronchial constriction of anesthetized male beagle dogs was studied (Nogami-Itoh et al. 1997). Bronchial constriction in the dogs was induced by the intravenous administration of histamine. The β2-agonist, salbutamol, in metered dose inhalers was used for treatment of the constriction. When HFC-134a was tested as the propellant for the salbutamol treatment (1-4 puffs of 100 or 200 μg of the drug), there was no effect of the HFC-134a on the salbutamol treatment compared to other CFC propellants. HFC-134a added to the formulation had no influence on histamine-induced bronchoconstriction, blood pressure or heart rate in the anesthetized dogs.

3.2.3. Rats

At 280,000 ppm there was a loss of righting reflex within 10 minutes (10-minute EC_{50}) (Collins, 1984). Rats exposed to 205,000 ppm were lethargic and exhibited an increased rate of respiration (Silber and Kennedy, 1979a). At 359,300 ppm, trembling and tearing also occurred. No effect was observed at 81,000 ppm.

Groups of 10 male rats were exposed to concentrations of 0, 10,000, 50,000, or 100,000 ppm for 6 hours/day, 5 days/week, for 2 weeks (Silber and Kennedy, 1979b). Five rats from each group were sacrificed at the end of the 10th exposure and the remaining five rats per group were sacrificed after a 14-day recovery period. No treatment related changes in weight gain, hematology parameters, blood chemistry, or organ weights were observed. An increased incidence of focal interstitial pneumonitis of the lung was the only adverse effect observed in the groups exposed to 50,000 and 100,000 ppm. The fluoride content of the urine was significantly increased in the treated rats.

TABLE 3. Summary of Sublethal Effects in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
monkey	500,000	1 minute	narcosis	Shulman and Sadove, 1967
dog	500,000 700,000	— 1 minute	light anesthesia deep anesthesia	Shulman and Sadove, 1967
rat	280,000	10 minutes	loss of righting reflex	Collins, 1984
rat	81,100 205,200 359,300	4 hours 4 hours 4 hours	no effect lethargy, rapid respiration lethargy, rapid respiration, trembling, tearing	Silber and Kennedy, 1979a
mouse	270,000 500,000	— <30 seconds	EC_{50}: loss of righting reflex narcosis	Shulman and Sadove, 1967

In a similar study, groups of 16 male and 16 female rats were exposed to concentrations of 0, 1000, 10,000, or 50,000 ppm 6 hours/day for 20 days of a 28-day period (Riley et al., 1979). No treatment-related effects were observed with regard to body weight, clinical signs, hematology, blood chemistry, urine composition, or ophthalmoscopy. In this study, changes in liver, kidney, and gonad weights of male rats in the group exposed to 50,000 ppm were noted with an increase in liver weight in the 10,000 ppm group also. In the absence of pathological changes in these organs, these weight changes were considered a physiological adaptation to treatment.

3.2.4. Mice

The EC_{50} for anesthetic effects measured by the loss of righting reflex was 270,000 ppm (Shulman and Sadove, 1967). At 500,000 ppm, induction time for narcosis was under 30 seconds and emergence time at cessation of administration was 10 seconds or less. These concentrations "appear(ed) to have no direct toxic effect."

3.3. Developmental/Reproductive Toxicity

In the 28-day study conducted by Riley et al. (1979), 16 male rats were exposed to HFC-134a at concentrations of 0, 1000, 10,000, or 50,000 ppm for 6 hours/day, 5 days/week. Rats exposed to 50,000 exhibited decreased gonad weights. However, in a 13-week study, no effects on male gonad weight were evident (see Section 3.2.3; Hext, 1989; Collins et al., 1995). In the chronic study (see Section 3.2.3; Collins et al., 1995), Leydig cell hyperplasia and benign Leydig-cell tumors were reported following exposure to 50,000 ppm for 104 weeks; no such effects were reported following exposure for 104 weeks to 10,000 ppm.

In a developmental study, Lu and Staples (1981) exposed pregnant CD rats to HFC-134a at concentrations of 30,000, 100,000, or 300,000 ppm for 6 hours/day from days 6 to 15 of gestation. Following exposure of dams to 300,000 ppm, there was a significant reduction in fetal weight and significant increases in several skeletal variations. At 300,000 ppm, signs of maternal toxicity included reduced food consumption, reduced body weight gain, lack of response to noise stimuli, severe tremors, and uncoordinated movements. Dams exposed to 100,000 ppm showed some signs including reduced response to noise stimuli and uncoordinated movements. No developmental effects were observed following exposure of dams to 30,000 or 100,000 ppm.

In a similar study, Hodge et al. (1979) exposed groups of pregnant rats to HFC-134a at concentrations of 0, 1000, 10,000, or 50,000 ppm for 6 hours/day on days 6 to 15 of gestation. No maternal toxicity was evident at these exposure concentrations, but at 50,000 ppm fetal body weight was significantly reduced and skeletal ossification was significantly delayed. The 10,000 ppm concentration was a NOEL.

Groups of 28 pregnant New Zealand white rabbits were exposed to concentrations of 0, 2500, 10,000, or 40,000 ppm for 6 hours/day on days 7 through 19 of pregnancy (Collins et al., 1995; Wickramaratne, 1989a,b). Dams were weighed during the study and sacrificed on day 29 of gestation. For each exposure group, various developmental parameters were compared with the control group: number of corpora lutea, number of implantations and live fetuses per female, percentage of pre- and postimplantation loss, percentage of implantations that were early or late intrauterine deaths, gravid uterus weight, litter weight, mean fetal weight, sex ratio, and percentage of fetuses with major or minor skeletal or visceral defects. No clinical signs were observed in the does. In the mid- and high-dose exposure groups, dams had a lower rate of body weight gain than the controls which was partially associated with decreased food consumption. With the exception of a significantly increased incidence of unossified seventh-lumbar transverse process in fetuses in the 10,000 and 40,000 ppm groups, all other parameters were similar among control and treatment groups. However, this effect was also observed in the control group and was therefore not considered treatment related. Therefore, there was no adverse developmental or teratogenic effect from exposure to HFC-134a.

Male and female AHA rats (of both Sprague-Dawley and Wistar origins) were exposed nose only to concentrations of 0 (filtered air), 2500, 10,000, or 50,000 ppm of "toxicology" grade HFC-134a (99.3% pure) for one hour daily throughout gametogenesis, mating, pregnancy, and lactation (Alexander et al., 1996). The "toxicology" grade of HFC-134a was formulated to contain all likely impurities. In the first part of the study, groups of 30 male and 30 female rats (F_0) were treated prior to mating (10 weeks for males and 3 weeks for females) and during mating. Treatment continued for males until sacrifice at week 18. Treatment continued for females until day 19 of pregnancy; 14 females were sacrificed on day 20 and fetuses were examined. The remaining females were allowed to deliver litters with no treatment between days 20 and day 1 *post partum*. On day 21 *post partum*, the F_0 females were sacrificed and examined along with some of their F_1 progeny. Selected F_1 rats were raised to maturity and mated. The survival and physical and functional development of the F_1 rats were assessed. Neurotoxicity (locomotor coordination, exploratory activity, and learning activity) was assessed between 4 and 9 weeks of age. The survival and physical development of the resulting F_2 progeny were also assessed. There were no adverse effects on the fertility of the F_0 generation and no adverse effects on the maturation and development of the F_1 and F_2 generations. The only treatment-related effect was a slight reduction in body weight gain of males of the F_0 generation in the 50,000 ppm group.

In the peri- and post-natal part of the study, groups of 41 female rats were administered concentrations of 1800, 9900, or 64,400 ppm of "toxicological" grade HFC-134a for 1 hour daily during days 17 to 20 of pregnancy and days 1 to 21 *post partum* (Alexander et al., 1996). The protocol was similar to that of the fertility study above. Females were allowed to litter and rear their young. Selected F_1 animals were mated; they were sacrificed on day 20 of pregnancy and the uterine contents were examined. There were no clinical signs or effects on body weights (F_0), corpora lutea, implants, numbers of live born pups, sex ratio, litter weights, fetal body weights, or development and survival of the F_1 generation. There was a small but significant delay in the occurrence of pinnae detachment, eye opening and startle response in the F_1 generation in the 64,400 ppm group. There were no visceral or skeletal abnormalities in the F_1 or F_2 generations.

3.4. Neurotoxicity

HFC-134a has anesthetic/narcotic action at high concentrations. As reported in Section 3.2, the 10-minute EC_{50} for anaesthetic effects in the rat was 280,000 ppm (Collins, 1984) and the EC_{50} in the mouse was 270,000 ppm (Shulman and Sadove, 1967). At concentrations of ~50% narcosis in dogs, cats, and monkeys takes only seconds to minutes (Shulman and Sadove, 1967). According to patent information, concentrations of at least 20% are required to have an aesthetic effect (Larsen, 1966).

In a study with rats involving several generations, locomotor activity was not affected by repeated treatment of the dams or young with concentrations up to 64,400 ppm (Alexander et al., 1996). The young were tested using an accelerating rotarod. Rats and mice were also tested after exposure for 18 months (Alexander et al., 1995). Rats were exposed to concentrations of 0, 2500, 10,000, or 50,000 ppm for 1 hour daily and mice were exposed to concentrations of 2500, 15,000, or 75,000 ppm also for 1 hour daily. The animals were examined on two consecutive days after 18 months of exposure (immediately after exposure on one day and 30 minutes after treatment on the following day) for effects on the central and/or peripheral nervous system using the modified Irwin screen test. There were no changes in behavior attributable to treatment.

3.5. Cardiac Sensitization

Mullin and Hartgrove (1979) evaluated the cardiac sensitization potential of HFC-134a with male beagle dogs (see Section 4.2 for Mechanism of Toxicity). Exposure concentrations were 50,000, 75,000,or 100,000 ppm. A fixed dose of epinephrine of 8 μg/kg was used pretest and as the challenge dose after 5 minutes of exposure to the test chemical. Cardiac responses (heart rate and EKG waves) were monitored with an electrocardiogram

throughout the experiment. No marked response was observed at an exposure of 50,000 ppm. Two of 10 dogs exhibited multiple ventricular beats during the exposures to 75,000 ppm and two of four dogs showed marked responses at 100,000 ppm, one with ventricular fibrillation leading to cardiac arrest.

Hardy et al. (1991) exposed a group of six male beagle dogs to concentrations of 40,000, 80,000, 160,000, or 320,000 ppm. Because the response to epinephrine alone varied among the dogs, the doses were adjusted to result in a few ectopic beats in the absence of the test chemical. Doses of epinephrine of 2, 4, or 8 μg/kg were administered. A marked response was considered five or more multifocal ventricular ectopic beats or ventricular fibrillation. Dogs that had a marked response at one concentration were not tested at higher concentrations. No cardiac sensitization occurred at 40,000 ppm. Two of six dogs responded at 80,000 ppm and one of the remaining four dogs (that did not test positive at 80,000 ppm) had convulsions at 160,000 ppm. Two of the remaining three dogs had marked responses at 320,000 ppm and the third suffered convulsions. Blood samples were taken just before administration of the second dose of epinephrine. The lowest concentration of HFC-134a that was associated with cardiac sensitization was 55 μg/mL.

TABLE 4. Cardiac Sensitization in Dogs Administered Exogenous Epinephrine[a]

Concentration (ppm)	Exposure Time	Response[b]	Reference
50,000 75,000 100,000	10 minutes 10 minutes 10 minutes	no response (10/10) marked response (2/10) marked response (1/4); death (1/4)	Mullin and Hartgrove, 1979
40,000 80,000 160,000 320,000	10 minutes 10 minutes 10 minutes 10 minutes	no response (6/6) marked response (2/6) convulsions (1/4) marked response (2/3); convulsions (1/3)	Hardy et al., 1991

[a]Animals were administered an intravenous dose of epinephrine of 8 μg/kg (Mullin and Hartgrove, 1979) or individualized doses of 2, 4 or 8 μg/kg (Hardy et al., 1991).
[b]A marked response is considered an effect; number of animals affected/number of animals tested in parenthesis.

3.6. Genotoxicity

HFC-134a has been tested in a variety of mutagenicity and clastogenicity tests, both *in vitro* and *in vivo*. These studies are summarized in Collins et al. (1995), ECETOC (1995), and the NRC Committee on Toxicology/Subcommittee to Review Toxicity of Alternatives to Chlorofluorocarbons (COT/SRTAC, 1996) and are listed here: bacterial mutation (*Salmonella typhimurium*, *Escherichia coli*, and *Saccharomyces cerevisiae*) with and without metabolic activation; chromosome aberrations (human lymphocytes, Chinese hamster lung cells, and inhalation study with the rat); micronucleus assay with the mouse (inhalation at test concentrations of 0, 50,000, or 150,000 ppm for 6 hours or 500,000 ppm for 5 hours); dominant lethal assay with the mouse (test concentrations of 0, 1000, 10,000, or 50,000 ppm for 6 hours/day for 5 days); and unscheduled DNA synthesis with the rat (test concentrations of 0, 10,000, 50,000, or 100,000 ppm for 6 hours). All results were negative.

3.7. Carcinogenicity

Groups of 20 male and 20 female Wistar-derived rats (Alpk:APfSD) were exposed to concentrations of 0, 2000, 10,000, or 50,000 ppm for 6 hours/day, 5 days/week for 13 weeks (Hext, 1989; Collins et al., 1995). Atmospheres were generated by evaporating the test compound and metering it into the air flow supply of each exposure chamber. Samples were automatically collected and analyzed by a gas chromatograph equipped with a flame ionization detector. Half of the animals in each group was sacrificed at the end of the exposure period and the remaining half was sacrificed after a 4-week recovery period. Survival, clinical condition, growth, and a variety of hematological, clinical chemistry, and urinary parameters were monitored. During the exposures there were no treatment-related clinical signs. Statistically significant changes in a few urine, blood, and hematological parameters and in organ weights were either not consistent with repeated sampling or dose related; there were no histological correlates.

In a similar study, groups of 85 male and 85 female rats were exposed to concentrations of 0, 2500, 10,000, or 50,000 ppm for 6 hours/day, 5 days/week for 104 weeks (Collins et al., 1995). Exposure conditions and analytical measurements were the same as in the 13-week study. Ten animals from each group were sacrificed at 52 weeks. At 52 and 104 weeks there were no effects on clinical condition, food consumption, growth, survival, or hematological, clinical chemistry, or urinary parameters. Absolute liver weights of females were increased in the groups exposed to 2500 and 50,000 ppm but not in the group exposed to 10,000 ppm. Males in the groups that received 10,000 or 50,000 ppm for 104 weeks had an increased incidence of enlarged testes (not statistically significant) and males in the group that received 50,000 ppm for 104 weeks had a statistically significantly increased incidence of Leydig cell hyperplasia (40 males vs 27 in the control group) and Leydig cell adenomas (23 males vs 9 in the control group). There was no evidence of progression to malignancy.

Groups of 60 male and 60 female Han-Ibm Wistar rats were exposed nose-only to vapor concentrations of 2500, 10,000, or 50,000 ppm of production grade HFC-134a for 1 hour daily for 108 weeks (Alexander et al., 1995). The 1-hour treatments were used to more closely simulate daily treatments from metered dose inhalers. There were no effects on survival, clinical signs, behavior (neurotoxicity), body weights, and hematology nor on the type, incidence, site or severity of gross or microscopic lesions or neoplasms. There was a dose-related increase in incidence and severity of “laryngitis” (not described) in female rats. In contrast to the study by Collins et al. (1995), there were no treatment related effects on Leydig cells.

Although there was an increased incidence of testicular Leydig cell adenomas in male rats administered 50,000 ppm for 104 weeks (Collins et al., 1995), these tumors do not progress to malignancy. The lack of genotoxicity also supports the conclusion of no carcinogenic risk for humans.

In a 52-week oral gavage study with Wistar-derived rats (36 males and 36 females per group), daily administration of 300 mg/kg in corn oil for 5 days/week did not result in an increased incidence of any type of tumors compared with corn-oil treated and untreated groups. Rats were sacrificed after 125 weeks (Longstaff et al., 1984).

Groups of 60 male and 60 female B6C3F1 mice rats were exposed nose-only to vapor concentrations of 2500, 10,000, or 50,000 ppm of production grade HFC-134a for 1 hour daily for 104 weeks (Alexander et al., 1995). The 1-hour treatments were used to more closely simulate daily treatments from metered dose inhalers. There were no effects on survival, clinical signs, behavior (neurotoxicity), body weights, hematology nor on the type, incidence, site or severity of gross or microscopic lesions or neoplasms.

3.8. Summary

HFC-134a has very low acute toxicity. In rats, lethal concentrations during exposure periods of 15 minutes to 4 hours ranged from >500,000 to >800,000 ppm (Collins, 1984; Silber and Kennedy, 1979a). Concentrations

of 200,000 ppm and greater induce anesthetic-like effects (Larsen, 1966). Monkeys, dogs and mice recovered without effects from anesthetic doses of 270,000 (mice) to 800,000 (dogs), the latter exposure lasting up to 5 hours (Shulman and Sadove, 1967).

In a subchronic study, no significant toxicological effects were observed in rats following inhalation exposure to 50,000 ppm (Collins et al., 1995). Likewise, in a chronic study with rats and exposures of 50,000 ppm, no effects other than testicular hyperplasia and benign tumors of Leydig cells were observed on microscopic examination (Collins et al., 1995). HFC-134a was not mutagenic or clastogenic in a variety of genetic toxicity tests.

Results from developmental studies indicate that HFC-134a does not cause teratogenic effects in rats or rabbits (Collins et al., 1995; Alexander et al., 1996). Fetotoxicity was observed in rats when dams were exposed to 50,000 ppm (Hodge et al., 1979). Slight maternal toxicity in rabbits as indicated by lower body weight gains compared to the control group were noted at 10,000 and 50,000 ppm (Collins et al., 1995). There was a slight delay in physical development of F_1 rats following exposure of F_0 females to 64,400 ppm (Alexander, 1996).

HFC-134a is a weak cardiac sensitizer in the epinephrine challenge test in dogs. Epinephrine-induced cardiac arrhythmias were observed at doses of 75,000 ppm and greater (Mullin and Hartgrove, 1979; Hardy et al., 1991). No cardiac response was observed at $\leq$50,000 ppm.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism/Disposition Considerations

4.1.1. Deposition and Elimination

Although absorption of fluorocarbons via inhalation is rapid with maximal blood concentrations reached in about 15 minutes, uptake is low (Azar et al., 1973; Trochimowicz et al., 1974; Mullin et al., 1979). Uptake approaches equilibrium in less than an hour; negligible metabolism and tissue uptake take place. Blood concentrations fall rapidly following cessation of exposure as the parent compound is exhaled basically unchanged.

In a study designed to gather pharmacokinetic data, two healthy human volunteers were exposed to a concentration of 4000 ppm delivered via a mouthpiece (Vinegar et al., 1997). The exposures were scheduled to last for 30 minutes. Blood samples were collected throughout the exposures. The exposures were abruptly terminated for safety reasons following an unexpected and uncontrollable rise in pulse rate for one subject and drop in pulse rate and blood pressure and loss of consciousness in the other. This vasovagal response is sometimes observed in individuals undergoing clinical investigations or donating blood. In the first subject the blood concentration of HFC-134a reached 0.7 mg/L (0.7 μg/mL) at 10 minutes and in the second subject the blood concentration reached 1.29 mg/L (1.29 μg/mL).

In the study with human subjects (Emmen and Hoogendijk, 1998; section 2.2), concentrations of the test chemical in blood were measured at 1, 3, 5, 15, 30, and 55 minutes into the exposure and postexposure. The mean blood concentrations in males at 55 minutes following exposures to concentrations of 1000, 2000, 4000, and 8000 ppm were 1.02, 1.92, 3.79, and 7.22 μg/mL, respectively; respective concentrations for females were 1.02, 1.44, 3.06, and 5.92 μg/mL. Concentrations rose rapidly during the first 15 minutes of exposure and were within 75-100% of levels measured at 55 minutes. The half-lives at the respective concentrations were males: 10.24, 12.69, 12.26, and 9.77 minutes and females: 11.36, 14.01, 13.20, and 16.69 minutes.

Absorption of radiolabeled HFC-134a delivered by metered dose inhalers to two healthy subjects was rapid with maximum blood concentrations of approximately 1.1 and 1.3 μg/mL attained within 30-60 seconds

(Ventresca, 1995). The half-life of elimination was 31 minutes. Retention in severe COPD patients was slightly longer than in healthy subjects and was attributed to their decreased ventilatory efficiency. The radioactivity recovered in urine was extremely low, 0.006% in healthy subjects and 0.004% in COPD patients. Uptake and elimination were similar in healthy subjects and subjects with mild asthma (Harrison, 1996). In another study with metered dose inhalers, blood levels of HFC-134a reached 717 ng/mL (0.72 μg/mL) and 1381 ng/mL (1.38 μg/mL) one minute after four and eight inhalations per day, respectively for 28 days. These levels decreased to one-tenth of the original level by 18 minutes postexposure (Harrison et al., 1996).

In pregnant female rats (Sprague-Dawley and Wistar strains) exposed nose only to concentrations of 2500, 10,000, and 50,000 ppm for 1 hour, maximum mean concentrations in the blood during exposure were 3.5, 13.9, and 84.7 μg/mL, respectively (Alexander et al., 1996). The half-life was 6-7 minutes. Following exposure of both male and female rats to 1 hour daily for 110 weeks, blood concentrations in the 2500, 10,000, and 50,000 ppm groups were 4.2-4.5, 16.5, and 62.3 μg/mL, respectively (Alexander et al., 1995). In male and female Sprague-Dawley rats exposed to a 15% atmosphere for 1 hour, the blood concentration approached equilibrium in 25 minutes (Finch et al., 1995). The half-life of elimination was <5 minutes as determined by magnetic resonance imaging.

In the 10-minute cardiac sensitization study with dogs, exposures to concentrations of 40,000, 80,000, 160,000, and 320,000 ppm resulted in mean blood concentrations of HFC-134a of 28.7, 52.2, 79.7, and 154.6 μg/mL, respectively (Hardy et al., 1991).

4.1.2. Metabolism

The carbon-fluorine bond is relatively resistant to metabolism. *In vitro* studies with rabbit, rat, and human hepatic microsomes and rat hepatocytes (Olson and Surbrook, 1991; Olson et al., 1990a, 1990b) identified the major route of metabolism of HFC-134a as oxidation by P450 2E1 to 2,2,2,1-tetrafluoroethanol; elimination of hydrogen fluoride or fluoride ion yields 2,2,2-trifluoroacetaldehyde which is further oxidized to trifluoroacetic acid. Hepatic microsome preparations from 12 human subjects differed in the rate at which HFC-134a was metabolized. In a study that utilized microsomes from human subjects with relatively high P-450 2E1 levels, HFC-134a was metabolized at rates 5 to 10-fold greater than by microsomes of individuals with lower levels of this enzyme (Surbrook and Olson, 1992).

Following delivery of 1200 mg of HFC-134a by inhalation from metered dose inhalers (16 actuations of 75 mg/inhalation; each inhalation within 30 seconds of the previous inhalation), the only fluorinated urinary component was trifluoroacetic acid which accounted for less than 0.0005% of the dose (Monte et al., 1994).

Metabolism in the rat is qualitatively similar to that in humans. Four male and four female Wistar rats were exposed individually to 10,000 ppm of ^{14}C-labeled HFC for one hour (Ellis et al., 1993). Atmospheres were monitored with a gas chromatograph. After exposure, urine and feces were collected at six hour intervals up to 24 hours and every 24 hours for up to 5 days thereafter. Approximately 1% of the inhaled dose was recovered in urine, feces, and expired air; of this 1%, approximately two-thirds was exhaled within one hour postexposure as unchanged HFC-134a. Exhaled CO_2 was the primary metabolite and accounted for approximately 0.22% and 0.27% of the inhaled dose in males and females, respectively. Excretion in the urine and feces occurred within 24 hours and accounted for 0.09% and 0.04% of the inhaled dose, respectively. The only metabolite identified in urine was trifluoroacetic acid. At sacrifice 5 days postexposure, radioactivity was uniformly distributed among tissues and accounted for 0.14-0.15% of the inhaled dose. The average total metabolism in males and females rats was 0.37% of the inhaled dose.

4.2. Mechanism of Toxicity

At high concentrations, HFC-134a has anesthetic/narcotic properties; cardiac sensitization may also occur. The mechanism(s) of action of these two effects is not well understood. The anesthetic effect was fully reversible.

Inhalation of certain hydrocarbons including some anesthetics can make the mammalian heart abnormally sensitive to epinephrine, resulting in cardiac (ventricular) arrhythmias which in some cases can lead to sudden death (Reinhardt et al. 1971). The mechanism of action of cardiac sensitization is not completely understood but appears to involve a disturbance in the normal conduction of the electrical impulse through the heart, probably by producing a local disturbance in the electrical potential across cell membranes. The hydrocarbons themselves do not produce arrhythmia; the arrhythmia is the result of the potentiation of endogenous epinephrine (adrenalin) by the hydrocarbon.

Although other species have been tested, the dog is the species of choice for the mammalian cardiac sensitization model as they are a good cardiovascular model for humans, have a large heart size, and can be trained to calmly accept the experimental procedures (Aviado, 1994; COT/SRTAC, 1996). The cardiac sensitization test has been evaluated by the COT/SRTAC (1996). They recommend that the male beagle dog be used as the model in this test.

Testing for cardiac sensitization consists of establishing a background (control) response to an injection of epinephrine followed by a second injection during exposure to the chemical of concern (Reinhardt et al., 1971). The dose of epinephrine chosen should be the maximum dose that does not cause a serious arrhythmia (COT/SRTAC). Because a second injection of epinephrine during air exposure often induces a mild cardiac response, Reinhardt et al. (1971) considered only "marked" responses to the second injection of epinephrine a significant cardiac sensitization response. Cardiac sensitization is defined as greater than five ectopic beats or ventricular fibrillation as evident on the EKG as a response to epinephrine. Ventricular tachycardia alone is not considered a positive response. The response to injected epinephrine lasts less than 60 seconds. Concentrations of halocarbons that do not produce a positive response in this short-term test generally do not produce the response when exposures are continued for 6 hours (Reinhardt et al., 1971; COT/SRTAC, 1996). This information indicates that cardiac sensitization is a concentration-related threshold effect. Furthermore, the exposure concentration-dependent level in the blood determines cardiac sensitization. The study by Hardy et al. (1991) indicated that for dogs this concentration is $\geq$55 μg/mL.

Although this test is useful for identifying compounds capable of cardiac sensitization, the capacity to establish an effect level is limited. The test is very conservative as the levels of epinephrine administered represent an approximate 10-fold excess over blood concentrations that would be achieved endogenously in dogs (Chengelis, 1997) or humans (COT/SRTAC, 1996) even in highly stressful situations. According to Mullin et al. (1979), the epinephrine dosage of 8-10 μg/kg/9 seconds is equivalent to 50-70 μg/kg/minute, whereas in times of stress, the human adrenal gland secretes levels of 4-5 μg/kg/minute. In earlier studies with dogs in which a loud noise was used to stimulate endogenous epinephrine release, arrhythmias occurred only at very high halocarbon concentrations (80% halocarbon compound and 20% oxygen) for 30 seconds (Reinhardt et al., 1971). In another study (Trochimowicz, 1997), the cardiac sensitization response was induced in exercising dogs at halocarbon concentrations that were 2 to 4 times the concentrations that induced the response with the exogenous epinephrine.

4.3. Structure-Activity Relationships

The halogenated hydrocarbons are generally of low acute toxicity, but several are associated with anesthetic

effects and cardiac sensitization. Cardiac sensitization to halogenated alkanes appears to be related to the number of chlorine or fluorine substitutions. Halogenated alkanes in which >75% of the halogens are fluorine are of low cardiac sensitization potential compared with halogenated alkanes in which ≥50% of the halogens are chlorine (Hardy et al., 1994). However, halogenation is not necessary for cardiac sensitization to occur (Reinhardt et al., 1971).

4.4. Concentration-Exposure Duration Relationship

Insufficient data were available to establish a concentration-exposure duration relationship for a single endpoint. LC_{50} values for the rat at 15 minutes and 4 hours were both several hundred thousand ppm (Table 2).

Time scaling may not be relevant for halogenated hydrocarbons as blood concentrations of these chemicals do not greatly increase as exposure time is increased beyond 15 minutes. In the study with human volunteers exposed to HFC-134a (Emmen and Hoogendijk, 1998), the relationship between exposure concentration and blood level appeared to be linear and at all exposure concentrations (1000, 2000, 4000, and 8000 ppm), blood concentrations were approaching equilibrium at 55 minutes. Furthermore, cardiac sensitization appears to be a concentration threshold phenomenon. Blood concentration which is related to exposure concentration rather than time defines whether or not a response will occur.

5. DATA ANALYSIS AND PROPOSED AEGL-1

The AEGL-1 refers to the concentration of an airborne substance below which the general population could be exposed without experiencing other than mild odor, taste, or other slight or mild sensory irritation, but at or above which persons might experience notable discomfort.

5.1. Summary of Human Data Relevant to AEGL-1

No effects were reported in humans exposed to concentrations of 1000, 2000, 4000, or 8000 ppm for one hour (Emmen and Hoogendijk, 1998). Concentrations of the test compound in blood appeared to approach equilibrium in <55 minutes. Following direct inhalation from metered dose inhalers, no effects were observed in either healthy subjects or patients with severe COPD (Ventresca, 1995).

5.2. Summary of Animal Data Relevant to AEGL-1

Animals were tested at much higher concentrations than those used in the human study. A concentration of 40,000 ppm was a no-effect concentration in the cardiac sensitization test with dogs (Hardy et al., 1991). No effects were observed in rats exposed to 81,000 ppm for 4 hours (Silber and Kennedy, 1979a). Repeated exposure of rats to a concentration of 100,000 for 6 hours/day, 5 days/week, for 2 weeks was without clinical signs (Silber and Kennedy, 1979b); the interstitial pneumonia observed in the treated group was not observed in other studies. Concentrations <200,000 ppm were a no-effect level for anesthetic effects in several species (Larsen, 1966; Shulman and Sadove, 1967).

5.3. Derivation of AEGL-1

The study with human subjects exposed to a concentration of 8000 ppm for 1 hour is the basis for the AEGL-1 values. This concentration-exposure duration was a no-effect level for irritation as well as lung and heart parameters. Although the 1-hour concentration of 8000 ppm is a free-standing NOEL, animal studies with several species indicate that this concentration is far below any effect level. Humans may differ in their

sensitivity to halocarbons, but no clear intraspecies differences were evident at this low concentration or in the study with COPD patients. Therefore, the 8000 ppm concentration was adjusted by an intraspecies uncertainty factor of 1.

Blood concentrations of halocarbons do not increase greatly with time after 15 minutes of exposure (COT/SRTAC) and rapidly drop following cessation of exposure; the data from the Emmen and Hoogendijk (1998) study support this observation. The unmetabolized compound is present in blood; HFC-134a is poorly absorbed and poorly metabolized by body tissues/organs. Because the pharmacokinetic data for humans show that blood concentrations do not increase greatly with time after 55 minutes, no greater effects (regarding cardiac sensitization) should be experienced at longer exposure intervals. Therefore, the 1-hour value of 8000 ppm is proposed for all AEGL-1 exposure durations (Table 5).

TABLE 5. AEGL-1 Values for HFC-134a

Time	AEGL-1 Value
10 minutes	8000 ppm (34,000 mg/m^3)
30 minutes	8000 ppm (34,000 mg/m^3)
1 hour	8000 ppm (34,000 mg/m^3)
4 hours	8000 ppm (34,000 mg/m^3)
8 hours	8000 ppm (34,000 mg/m^3)

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The NOEL value of 8000 ppm is supported by results of animal studies. No effects were observed in rats exposed to 81,100 ppm for 4 hours (Silber and Kennedy, 1979a). Adjustment by interspecies and intraspecies uncertainty factors of 3 and 3 (10) result in an AEGL value of ~8000 ppm.

6. DATA ANALYSIS AND PROPOSED AEGL-2

The AEGL-2 refers to the concentration at or above which the general population could experience irreversible or other serious long-lasting effects or impaired ability to escape.

6.1. Summary of Human Data Relevant to AEGL-2

No human data that address the level of effects defined by the AEGL-2 were located.

6.2. Summary of Animal Data Relevant to AEGL-2

Humans exposed to high concentrations of some halogenated hydrocarbons may develop heart arrhythmias which are potentially fatal. The cardiac sensitization test in dogs is an effective test for determining potential cardiac sensitization in humans. This effect is observed at concentrations well below those causing any acute toxic signs but only in the presence of greater than physiological doses of exogenous epinephrine.

In the cardiac sensitization with dogs conducted by Hardy et al. (1991), doses of epinephrine were adjusted for each dog to a point at which a mild response occurred in the absence of the test chemical. This individualized dose provides a more realistic test than delivery of a flat dose to each animal. In this study, a second exogenous

dose of epinephrine during exposure to HFC-134a did not produce cardiac sensitization (more than the mild effect) at an exposure concentration of 40,000 ppm; cardiac sensitization (a marked response) was induced in two of six dogs at an exposure concentration of 80,000 ppm.

6.3. Derivation of AEGL-2

Although it is an optimized, supersensitive model, the endpoint of cardiac sensitization is relevant to human exposures as humans exposed to high concentrations of some halocarbons develop cardiac arrhythmias. The no-effect concentration of 40,000 ppm was accepted as the basis for the AEGL-2 values. Because this is a conservative test, an intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. Because blood concentrations were close to equilibrium within 55 minutes during human exposures and concentrations of halocarbons that do not produce a positive response in the short-term cardiac sensitization test do not produce the response when exposures are continued for 6 hours, the value of 13,000 ppm (13,300 ppm rounded to two significant figures) is proposed for all AEGL-2 time periods (Table 6).

TABLE 6. AEGL-2 Values for HFC-134a

Time	AEGL-2 Value
10 minutes	13,000 ppm (55,250 mg/m^3)
30 minutes	13,000 ppm (55,250 mg/m^3)
1 hour	13,000 ppm (55,250 mg/m^3)
4 hours	13,000 ppm (55,250 mg/m^3)
8 hours	13,000 ppm (55,250 mg/m^3)

The AEGL-2 value is supported by an animal toxicity study which produces a higher value. The threshold for narcosis for several animal species is ~200,000 ppm (Collins, 1984; Silber and Kennedy, 1979a). The value is probably similar for humans. Adjustment by interspecies and intraspecies uncertainty factors of 3 each (for a total of 10) results in an AEGL-2 value of 20,000 ppm.

7. DATA ANALYSIS AND PROPOSED AEGL-3

The AEGL-3 refers to the concentration at or above which death or life-threatening effects may occur.

7.1. Summary of Human Data Relevant to AEGL-3

No human data that address the level of effects defined by the AEGL-3 were located.

7.2. Summary of Animal Data Relevant to AEGL-3

Humans exposed to high concentrations of some halogenated hydrocarbons may develop heart arrhythmias which are potentially fatal. The cardiac sensitization test in dogs is an effective test for determining potential cardiac sensitization in humans. This effect is observed at concentrations well below those causing any acute toxic signs but only in the presence of greater than physiological doses of exogenous epinephrine.

In the cardiac sensitization study with dogs conducted by Hardy et al. (1991), doses of epinephrine were adjusted for each dog to a point at which a mild response occurred in the absence of the test chemical. This individualized dose provides a more realistic test than delivery of a flat dose to each animal. In this study, a second exogenous dose of epinephrine during exposure to HFC-134a did not produce cardiac sensitization (more than the mild effect) at an exposure concentration of 40,000 ppm; cardiac sensitization (a marked response) was induced in two of six dogs at an exposure concentration of 80,000 ppm. The dose that results in death could not be ascertained in this study as dogs were not tested at doses higher than those causing the marked response. Death occurred in the Mullin and Hartgrove (1979) study at a concentration of 100,000 ppm, but doses were not individualized (the highest dose of epinephrine [8 μg] was used for all dogs).

7.3. Derivation of AEGL-3

Although it is an optimized, supersensitive model, the endpoint of cardiac sensitization is relevant to human exposures as humans exposed to high concentrations of some halocarbons may develop cardiac arrhythmias. The concentration of 80,000 ppm which induced a marked cardiac response in the dog was used as the basis for the AEGL-2 values. Because the cardiac sensitization test is a conservative test, an intraspecies uncertainty factor of 3 was applied to protect sensitive individuals. Because blood concentrations were close to equilibrium within 55 minutes during human exposures and concentrations of halocarbons that do not produce a positive response in the cardiac sensitization test do not produce the response when exposures are continued for 6 hours, the value of 27,000 ppm (26,600 ppm rounded to two significant figures) is proposed for all AEGL-3 time periods (Table 7).

TABLE 7. AEGL-3 Values for HFC-134a

Time	AEGL-3 Value
10 minutes	27,000 ppm (114,750 mg/m^3)
30 minutes	27,000 ppm (114,750 mg/m^3)
1 hour	27,000 ppm (114,750 mg/m^3)
4 hours	27,000 ppm (114,750 mg/m^3)
8 hours	27,000 ppm (114,750 mg/m^3)

The AEGL-3 value is supported by another animal study which results in a higher value. The highest nonlethal concentration for the rat was a 4-hour exposure to 359,300 ppm (Silber and Kennedy, 1979a). Adjustment by interspecies and intraspecies uncertainty factors of 3 each (for a total of 10) results in an AEGL-3 value of ~36,000 ppm. Developmental studies in which exposures were repeated for 9-13 days also support this value, i.e., no effects following daily exposures to concentrations <30,000 ppm.

8. SUMMARY OF PROPOSED AEGLs

8.1. AEGL Values and Toxicity Endpoints

In summary, the AEGL values for various levels of effects were derived using the following methods. The AEGL-1 was based on a 1-hour no effect level of 8000 ppm in human subjects. Because effects occurred in animal studies only at considerably higher concentrations, an intraspecies uncertainty factor of 1 was applied.

Because blood concentrations had approximately reached equilibrium 55 minutes into the exposure and blood concentrations determine the level of effect, the 8000 ppm concentration was used across all time periods.

The AEGL-2 was based on the threshold for cardiac sensitization using the dog model. Because this test is supersensitive as the response to epinephrine is optimized, the 40,000 ppm concentration was adjusted by a single intraspecies uncertainty factor of 3 to protect sensitive individuals. Because blood concentrations rapidly reach equilibrium and the blood concentration determines the level of effect, the 13,000 ppm value was used across all time periods.

The AEGL-3 was based on the lowest response that induced a marked cardiac effect in the cardiac sensitization test with the dog. This concentration of 80,000 was adjusted by a single intraspecies uncertainty factor of 3 to protect sensitive individuals. An interspecies uncertainty factor was not applied as this is a supersensitive test. Because blood concentrations rapidly reach equilibrium and the blood concentration determines the level of effect, the 27,000 ppm value was used across all time periods.

The AEGL values are summarized in Table 8.

TABLE 8. Summary/Relationship of AEGL Values

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)	8000 ppm (34,000 mg/m^3)
AEGL-2 (Disabling)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)	13,000 ppm (55,250 mg/m^3)
AEGL-3 (Lethal)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)	27,000 ppm (114,750 mg/m^3)

8.2. Comparisons with Other Standards and Criteria

Standards and guidelines developed by other agencies are listed in Table 9. HFC-134a is a relatively new chemical and only the American Industrial Hygiene Association (AIHA, 1991) has developed workplace guidelines. The AIHA WEEL (Workplace Environmental Exposure Level) is an 8-hour time-weighed average.

For establishment of a 1-hour EEGL (Emergency Exposure Guidance Level), the COT/SRTAC (1996; Bakshi, 1998) recommended application of a single interspecies factor of 10 to the cardiac sensitization test with the dog. Because blood concentrations of several halocarbons rapidly reached equilibrium, the Subcommittee also extrapolated this 10-minute test to the longer exposure duration of 1 hour. The Subcommittee proposed a 24-hour EEGL of 1000 ppm based on the NOAEL of 10,000 ppm for fetoxicity in the study by Hodge et al., (1979). The 10,000 ppm concentration was adjusted by an uncertainty factor of 10 for interspecies variability. It should be noted that the study with human subjects (Emmen and Hoogendijk, 1998) was not available to the COT/SRTAC.

The U.S. EPA (1995) has derived a Reference Concentration (RfC) of 80 mg/m^3 (19 ppm) for this chemical

based on the NOAEL of 10,000 ppm for Leydig cell hyperplasia in the rat chronic inhalation study of Collins et al. (1995).

TABLE 9. Standards and Guidelines for HFC-134a

Agency/Organization	Exposure Concentration
ACGIH TLV-TWA	Not established
ACGIH TLV-CEILING	Not established
AIHA WEEL (AIHA 1991)	1000 ppm
OSHA PEL-TWA	Not established
OSHA PEL-STEL	Not established
NIOSH REL-TWA	Not established
NIOSH STEL	Not established
NIOSH IDLH	Not established
1-hour EEGL (COT/SRTAC, 1996)	4000 ppm
24-hour EEGL (COT/SRTAC, 1996)	1000 ppm
ERPG-1	Not established
ERPG-2	Not established
ERPG-3	Not established
German MAK	1000 ppm

8.3. Confidence in the Proposed AEGLs

Confidence in the proposed values is high as the studies involved both human subjects and animal models; covered acute, subchronic, and chronic exposure durations; and addressed systemic toxicity as well as neurotoxicity, reproductive and developmental effects, cardiac sensitization, genotoxicity, and carcinogenicity. The metabolism of HFC-134a is well understood and the relationship of exposure concentration to blood concentration (and effect) has been addressed in both the human and the rodent.

8.4. Data Deficiencies

No data deficiencies were apparent.

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ACUTE EXPOSURE GUIDELINE LEVELS FOR 1,1,1,2-TETRAFLUOROETHANE (HFC-134a; CAS NO. 811-97-2)

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
8000 ppm	8000 ppm	8000 ppm	8000 ppm	8000 ppm

Key Reference: Emmen, H.H., and E.M.G. Hoogendijk. 1998. Report on an ascending dose safety study comparing HFA-134a with CFC-12 and air, administered by whole-body exposure to healthy volunteers. MA-250B-82-306, TNO Report V98.754, The Netherlands Organization Nutrition and Food Research Institute, Zeist, The Netherlands.

Test Species/Strain/Number: Eight healthy adult human subjects

Exposure Route/Concentrations/Durations: Inhalation: 0, 1000, 2000, 4000, 8000 ppm for 1 hour.

Effects: No effects on tested parameters of blood pressure, heart rate, electrocardiogram (EKG) rhythms, or lung peak expiratory flow.

Endpoint/Concentration/Rationale: The highest no-effect concentration of 8000 ppm for 1 hour was used as the basis for the AEGL-1. This concentration is considerably below the threshold for effects in animal studies. For example, anesthetic effects occur at a concentration of ~200,000 ppm.

Uncertainty Factors/Rationale:
Total uncertainty factor: 1
Interspecies: Not applicable, human subjects used.
Intraspecies: 1 - This was a no-effect level for eight healthy individuals . At these low exposure concentrations, there was no indication of differences in sensitivity among the subjects.

Modifying Factor: Not applied.

Animal to Human Dosimetric Adjustment: Not applied, human subjects used.

Time Scaling: Not applied. Effects such as cardiac sensitization have been correlated with blood concentrations. Several studies have shown that blood concentrations of halocarbons do not increase greatly with time after 15 minutes of exposure. The key study showed that at each exposure concentration, blood concentrations were approaching equilibrium after 55 minutes of exposure. Therefore, susceptibility to effects are predicted to remain the same as exposure time increases beyond 1 hour.

Confidence and Support for AEGL-Values: The study was well conducted and documented.

AEGL-2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
13,000 ppm	13,000 ppm	13,000 ppm	13,000 ppm	13,000 ppm

Key Reference: Hardy, C.J., I.J. Sharman, and G.C. Clark. 1991. Assessment of cardiac sensitisation potential in dogs: comparison of HFA 134a and A12. Report No CTL/C/2521, Huntingdon Research Centre, Cambridgeshire, U.K.

Test Species/Strain/Sex/Number: Male beagle dogs, six total.

Exposure Route/Concentrations/Durations: Inhalation: 40,000, 80,000, 160,000, or 320,000 ppm for ten minutes (the cardiac sensitization test is a 10-minute exposure test). The test is based on the principal that halocarbons make the mammalian heart abnormally sensitive to epinephrine. Epinephrine is administered prior to and during test exposures at doses that are up to 10 times higher than levels secreted by the human adrenal gland in time of stress. Doses of epinephrine were adjusted for each individual dog so that administration without the test chemical produced a threshold response.

Effects:

Concentration (ppm)	Response
40,000	no response
80,000	marked response (2/6)
160,000	convulsions (1/4)
320,000	marked response (2/3); convulsions (1/3)

A marked response is considered an effect; number of dogs affected/number of dogs tested in parenthesis. Dogs that responded at one concentration were not tested at higher concentrations.

Endpoint/Concentration/Rationale: The no-effect concentration of 40,000 ppm was chosen as the basis for the AEGL-2 because the next higher concentration of 80,000 ppm produced a serious effect.

Uncertainty Factors/Rationale:
Total uncertainty factor: 3
- Interspecies: 1 - The cardiac sensitization model with the dog heart is considered a good model for humans.
- Intraspecies: 3 - The test is optimized; there is a built in safety factor because of the greater than physiological dose of epinephrine administered. In addition, there is no data indicating individual differences in sensitivity.

Modifying Factor: Not applied.

Animal to Human Dosimetric Adjustment: Not applied. As noted, the cardiac sensitization model with the dog heart is considered a good model for humans.

Time Scaling: Not applied. Cardiac sensitization is an exposure and blood concentration related threshold effect. Several studies have shown that blood concentrations of halocarbons do not increase greatly with time after 15-55 minutes of exposure and exposure duration did not influence the concentration at which the effect occurred.

Confidence and Support for AEGL Values: The study was well conducted and documented. Other effects in animal studies occurred at much higher concentrations or with repeated exposures; the latter are not relevant for setting short-term exposures.

AEGL-3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
27,000 ppm	27,000 ppm	27,000 ppm	27,000 ppm	27,000 ppm

Key Reference: Hardy, C.J., I.J. Sharman, and G.C. Clark. 1991. Assessment of cardiac sensitisation potential in dogs: comparison of HFA 134a and A12. Report No CTL/C/2521, Huntingdon Research Centre, Cambridgeshire, U.K.

Test Species/Strain/Sex/Number: Male beagle dogs, six total.

Exposure Route/Concentrations/Durations: Inhalation: 40,000, 80,000, 160,000, or 320,000 ppm for ten minutes (the cardiac sensitization test is a 10-minute exposure test). The test is based on the principal that halocarbons make the mammalian heart abnormally sensitive to epinephrine. Epinephrine is administered prior to and during test exposures at doses that are up to 10 times higher than levels secreted by the human adrenal gland in time of stress. Doses of epinephrine were adjusted for each individual dog so that administration without the test chemical produced a threshold response.

Effects:

Concentration (ppm)	Response
40,000	no response
80,000	marked response (2/6)
160,000	convulsions (1/4)
320,000	marked response (2/3); convulsions (1/3)

A marked response is considered an effect; number of dogs affected/number of dogs tested in parenthesis. Dogs that responded at one concentration were not tested at higher concentrations.

Endpoint/Concentration/Rationale: The concentration of 80,000 ppm was chosen as the basis for the AEGL-2 because it produced a serious, life-threatening cardiac arrhythmia in two of six dogs. No dogs died at this or the two higher concentration although one of four dogs suffered convulsions at 160,000 ppm and one of three dogs suffered convulsions at 320,000 ppm. The latter tests were discontinued.

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1 - The cardiac sensitization model with the dog heart is considered a good model for humans.

Intraspecies: 3 - The test is optimized; there is a built in safety factor because of the greater than physiological dose of epinephrine administered. In addition, there is no data indicating individual differences in sensitivity.

Modifying Factor: Not applied.

Animal to Human Dosimetric Adjustment: Not applied. As noted, the cardiac sensitization model with the dog heart is considered a good model for humans.

Time Scaling: Not applied. Cardiac sensitization is an exposure and blood concentration related threshold effect. Several studies have shown that blood concentrations of halocarbons do not increase greatly with time after 15-55 minutes of exposure and exposure duration did not influence the concentration at which the effect occurred.

Confidence and Support for AEGL Values: The study was well conducted and documented. Other effects in animal studies occurred at much higher concentrations or with repeated exposures; the latter are not relevant for setting short-term exposures.